Amebiasis Presenting as Pleuropulmonary Disease

KENNETH R. KUBITSCHEK, MD; JAY PETERS, MD; DAVID NICKESON, MD, *and* DANIEL M. MUSHER, MD, *Houston*

Seven patients with amebic liver abscess presenting as pleuropulmonary disease were admitted to hospital initially because of pulmonary symptoms and were found to have amebic liver disease. Three categories of pleuropulmonary involvement included reactive inflammation of the pleura or lung, rupture of a hepatic abscess into the pleural space and rupture of a hepatic abscess into the bronchial airways. The preferred medical treatment is with metronidazole, but rupture of a hepatic amebic abscess into the pleural space requires drainage in addition to medical therapy. In contrast, rupture into the bronchus may provide spontaneous drainage so that only medical therapy is needed. Recovery from amebiasis in all three categories is generally complete. Morbidity and mortality increase with failure to correctly identify amebic infection of the liver as the underlying cause. Because, in new cases, no findings specifically suggest that pleuropulmonary disease is a complication of hepatic amebic abscess, this possibility needs to be considered, especially in persons who are at risk of having been infected with amebae.

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Extraintestinal amebiasis occasionally presents as pleuropulmonary disease with few clues to suggest the presence of an underlying hepatic abscess[1]; in such cases, the correct diagnosis may be reached only with great difficulty and after considerable delay.[1-3] We report the cases of seven patients whose presenting symptoms led to a primary consideration of intrathoracic disease, but who, in fact, had pleuropulmonary complications of amebic liver abscess. These complications fell into one of three pathophysiologic categories: (1) reactive inflammatory response of the pleura or lung resulting in pleural effusion or pneumonitis—in this situation, the hepatic abscess being confined to the liver; (2) rupture of the abscess into the pleural space resulting in empyema, and (3) erosion directly into the bronchial airways, resulting in consolidation, lung abscess or hepatobronchial fistula, with or without a pleural effusion or empyema. This study emphasizes the need to consider amebic infections in the evaluation of thoracic complaints, especially in recent Latin-American immigrants and travelers returning from endemic areas.

Patients

The seven patients described here were referred for pulmonary consultation at one of the Baylor College of Medicine-affiliated hospitals during the 18-month period from December 1980 to May 1982. The clinical course, laboratory data, roentgenographic data and treatment of each are summarized in Table 1.

The mean age of the five men and two women was 39 years (range, 21 to 70). Six of the seven were Mexican immigrants who had resided in the United States for an average of 15.6 months (range, 5 to 36) before admission. The seventh patient had traveled to Mexico three months before he became ill.

Pulmonary symptoms, generally subacute in nature, represented the chief complaint in all patients. These included chest pain (three patients), dyspnea (one), persistent cough (one), hemoptysis (one) and thick, "chocolate" sputum (one). After the diagnosis of amebiasis had been established, a vague history of abdominal symptoms such as abdominal

From the Medical Service (General Medicine, Pulmonary Disease and Infectious Disease Sections), Veterans Administration Medical Center, Houston, and the Department of Medicine, Baylor College of Medicine, Houston.
Submitted, revised, March 26, 1984.
Reprint requests to Kenneth R. Kubitschek, MD, General Medicine Section, VA Medical Center, 2002 Holcombe Blvd, Houston, TX 77211.

ABBREVIATIONS USED IN TEXT

CIE = counterimmunoelectrophoresis
CT = computed tomography
LDH = lactic dehydrogenase
P_{CO_2} = partial carbon dioxide pressure
P_{O_2} = partial oxygen pressure

pain was elicited in three patients. The average duration of illness before admission was 43.5 days with a broad range (5 to 120).

Four of the seven patients had a fever (temperature greater than 38.3°C [101°F]) at presentation; two others became febrile during their hospital stay. One patient remained afebrile throughout his course. Physical findings consistent with pleural effusion or pneumonia, or both, were noted in every case. On abdominal examination two patients were found to have upper abdominal tenderness. The liver was not thought to be enlarged in any of the seven cases. All of the patients had leukocytosis with a mean leukocyte count of 16,900 per μl (range, 11,200 to 20,000). Liver function tests showed minimal abnormalities in six patients and essentially no abnormalities in the seventh. Liver scans showed a solitary right lobe defect in six patients. In the seventh patient, an abdominal computed tomographic (CT) scan showed a large, left upper quadrant abscess contiguous with the liver. All seven patients had antibody to amebic antigens detected by counterimmunoelectrophoresis (CIE).

In the seven patients there was a total of 12 pleuropulmonary complications (Table 1). These included three cases of inflammatory pleural reaction with effusion; two episodes of rupture into the pleural space with empyema, and seven episodes of rupture into the airways resulting in consolidation (two), abscess (three) and hepatobronchial fistula (two). In two patients, the diagnosis of amebiasis was made only after an exploratory operation. All seven patients responded promptly to treatment with metronidazole and were asymptomatic at the time of discharge. Three illustrative cases are presented below.

Reports of Cases

Case 1. Reactive Pleural Effusion

Three months before the present admission this 42-year-old Mexican man (patient 1, Table 1) was evaluated for chest pain and found to have a left-sided pleural effusion. Diagnostic thoracentesis showed an exudative fluid that was sterile and contained no tumor cells. A presumptive diagnosis of tuberculosis was made and isoniazid and rifampin therapy was begun. On this therapy his symptoms worsened and he was readmitted to hospital with chest pain and fever. The peripheral leukocyte count was 17,800 per μl, the serum alkaline phosphatase was 151 IU per liter and the albumin was 3.0 grams per dl. Other liver function studies did not show abnormalities. The chest roentgenogram showed a left pleural effusion and an elevated hemidiaphragm. An abdominal CT scan showed a left subphrenic abscess contiguous with the left lobe of the liver. The pleural effusion was again sterile and contained 5.9 grams per dl protein, 79 IU per liter lactic dehydrogenase (LDH) and 4,600 leukocytes per μl, of which 30% were polymorphonuclear leukocytes. The diagnosis of amebiasis was not considered.

On exploratory laparotomy a large left upper quadrant abscess was found and drained. *Entamoeba histolytica* was seen in the aspirated material and metronidazole, 750 mg, was initially given parenterally every eight hours for two days and orally thereafter. Additionally, both Gram-nega-

TABLE 1.—*Clinical, Laboratory and Therapeutic Data on Patients With Pleuropulmonary Amebiasis*

Patient	*Age,Sex*	*Chief Complaint*	*Other Complaints*	*Bilirubin* mg/dl*	*AST* IU/liter*	*ALT* IU/liter*	*Alk Phos* IU/liter*	*Chest X-ray*	*Abdominal Scan*	*Pleuropulmonary Complication(s)*	*Treatment*
1	42 ♂	Left chest pain	LUQ pain, Fever	0.4	13	29	151	Left pleural effusion; elevated left diaphragm	CT: left subphrenic abscess contiguous with liver	Reactive pleural effusion	Exploratory laparotomy, metronidazole
2	27 ♀	Right chest pain	Dyspnea	0.4	56	78	...	Opacified right lung	Liver scan: cold defect	Empyema	Tube thoracostomy, metronidazole
3	70 ♀	Right chest pain	RUQ pain, Anorexia, Weight loss	0.5	13	9	130	Loculated right pleural effusion	Liver scan: cold defect	Empyema	Tube thoracostomy, metronidazole
4	27 ♂	Hemoptysis	Fever Weight loss, Night sweats	0.2	17	22	101	LLL infiltrate	Liver scan: cold defect	Consolidation, hepatobronchial fistula	LLL lobectomy, metronidazole
5	21 ♂	Persistent cough	RUQ pain, Anorexia	0.4	66	118	302	Air fluid level RLL, pleural thickening	Liver scan: cold defect	Lung abscess	Metronidazole
6	41 ♂	Chocolate sputum	None	0.6	19	25	231	RLL cavity, right pleural effusion	Liver scan: cold defect	Lung abscess, hepatobronchial fistula, reactive pleural effusion	Metronidazole
7	45 ♂	Dyspnea	None	2.0	162	63	159	RLL/RML cavity and infiltrate, right pleural effusion	Liver scan: cold defect	Lung abscess, consolidation, reactive pleural effusion	Metronidazole

LUQ = left upper quadrant, CT = computed tomography, RUQ = right upper quadrant, LLL = left lower lobe, RLL = right lower lobe, RML = right middle lobe

*Normal values: bilirubin, 0 to 1.1 mg/dl; AST = aspartate aminotransferase (or, glutamic oxaloacetic transaminase), 7 to 40 IU/liter; ALT = alanine aminotransferase (or, glutamic pyruvic transaminase), 7 to 40 IU/liter; Alk Phos = alkaline phosphatase, 30 to 115 IU/liter.

tive and Gram-positive organisms were noted and treatment with tobramycin and ticarcillin disodium was begun. Subsequent cultures grew *Escherichia coli* and three species of *Bacteroides*. Counterimmunoelectrophoresis showed serum antibodies to *E histolytica*. The patient's condition improved within 48 hours after therapy was initiated. The left pleural effusion resolved and he was discharged without symptoms 24 days later.

Case 2. Amebic Rupture into the Pleural Space

The patient, a 27-year-old Mexican woman (patient 2), had resided in the United States for 12 months when she was admitted to hospital with a two-day history of severe, right-sided pleuritic chest pain and dyspnea. On admission her temperature was 38.5°C (101.3°F) and on physical examination she had findings of a right-sided pleural effusion. The abdominal examination showed no abnormalities. Laboratory studies showed a leukocyte count of 18,000 per μl and minimally abnormal liver function. Arterial blood gases done with the patient breathing room air showed a pH of 7.47, partial carbon dioxide pressure (P_{CO_2}) 30.5 mm of mercury and partial oxygen pressure (P_{O_2}) 54 mm of mercury. A chest roentgenogram showed opacification of the right lower hemithorax.

The initial diagnosis was pneumonia or pulmonary embolism and she was treated with penicillin and heparin. The next day the entire right lung field was opacified. A diagnostic thoracentesis showed chocolate-colored purulent material with a protein of 4.0 grams per dl, LDH 3,340 IU per liter, glucose 93 mg per dl and amylase 55 mg per dl. This material contained no bacteria on direct examination or culture. The serum was strongly positive for antibodies to *E histolytica* by CIE. On ultrasonography there was an 8.6 by 11 cm filling defect in the right posterior lobe of the liver. Administration of metronidazole, 750 mg by mouth every eight hours, was begun and a right tube thoracostomy drained 860 ml of purulent material. The patient's symptoms resolved over 36 hours, and she was discharged with a chest tube in place. Two months later she underwent decortication for an entrapped lung. Nine weeks thereafter she was asymptomatic and the chest roentgenogram showed minimal fibrotic changes. Ultrasonography showed that the abscess cavity in the liver had resolved.

Case 3. Amebic Rupture Into the Bronchial Airways

The patient, a 27-year-old Mexican man (patient 4), was admitted to hospital after four months of intermittent hemoptysis, fever, night sweats and a weight loss of 9 kg (20 lb). He had no abdominal pain or diarrhea. His temperature was 38.7°C (101.7°F) and he had dullness to percussion and rales in the left base. Laboratory studies showed a leukocyte count of 19,300 per μl and normal liver function. Chest x-ray films showed a left lower lobe infiltrate with consolidation (Figure 1). Sputum cultures yielded no pathogenic bacteria and bronchoscopy was negative. A diagnosis of tuberculosis was made and treatment with isoniazid and rifampin was begun. The hemoptysis and fever persisted and he underwent a left lower lobectomy. Surgical exploration showed an abscess with a sinus tract leading to the right lobe of the liver. *Entamoeba histolytica* was found in the resected tissue.

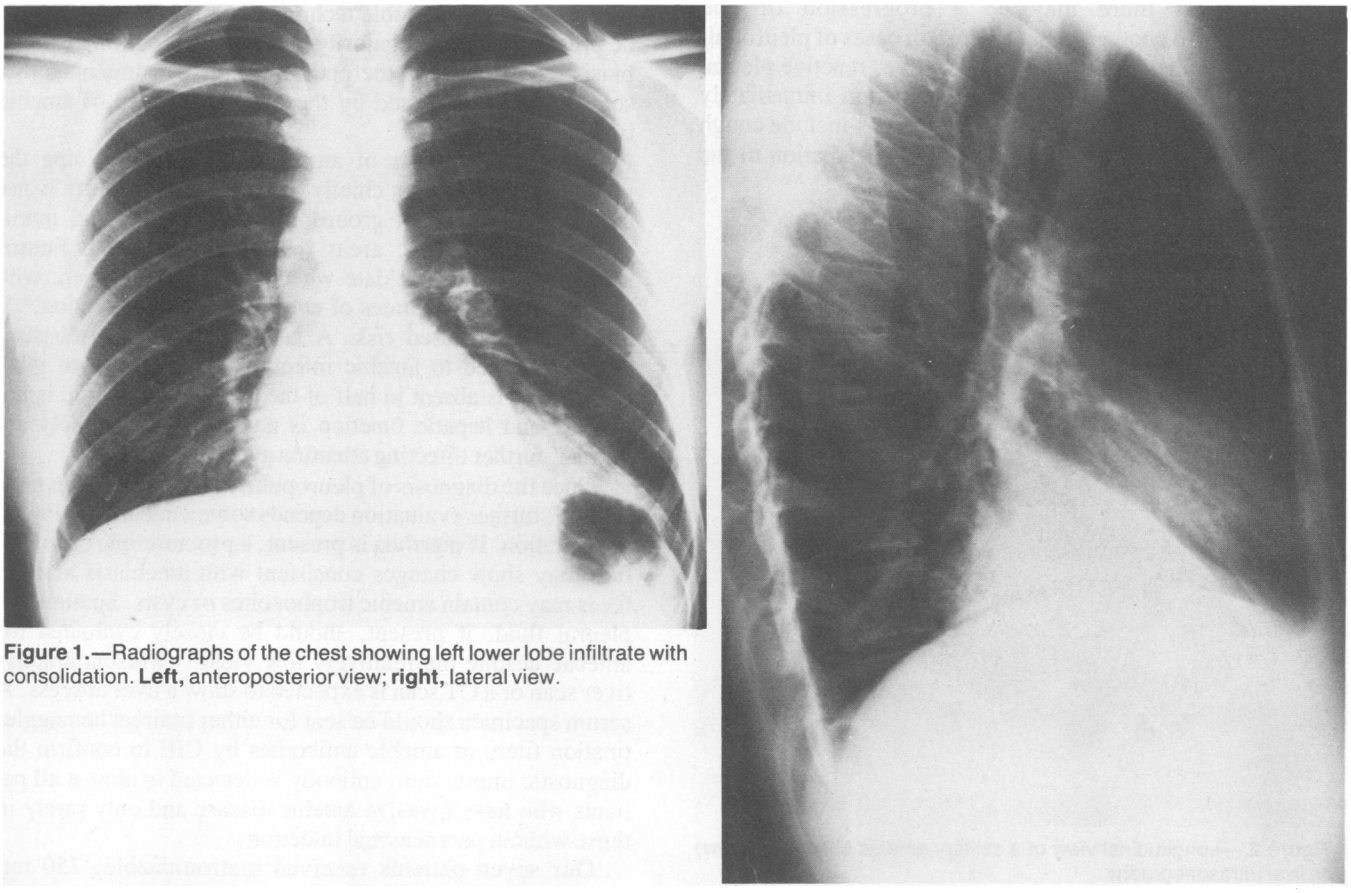

Figure 1.—Radiographs of the chest showing left lower lobe infiltrate with consolidation. **Left,** anteroposterior view; **right,** lateral view.

After the surgical procedure, CIE showed serum antibodies to *E histolytica.* On ultrasonography (Figure 2) and a liver-spleen scan, a single abscess was found in the right lobe of the liver. Metronidazole, 750 mg, was given orally every eight hours with prompt improvement. He was discharged without symptoms 14 days later. Two months later the patient was still healthy, although an ultrasound examination and liver-spleen scan showed a residual hepatic defect.

Discussion

Our seven patients had symptoms that were typical of the previously reported pleuropulmonary complications of amebiasis.[2,4,5] The prodromal symptoms were insidious in onset. Complaints of abdominal pain, weakness, weight loss and anorexia were vague and were elicited only in retrospect after the correct diagnosis had been established. The major symptoms were referable to the thorax. These included shortness of breath, cough and pleuritic chest pain. Whereas the onset of symptoms in some patients suggested an acute inflammatory process, in others the insidious nature of the symptoms was more suggestive of a chronic wasting disease. The diagnosis of tuberculosis was frequently suggested both because of the symptoms and because the patients came from areas where there tended to be a high incidence of endemic tuberculosis. Physical findings similarly pointed to intrathoracic disease. It is important to emphasize that the liver was not enlarged in any of our patients, tenderness over the liver was absent and laboratory studies showed such minimal abnormalities that the liver was not thought to be involved.

Three kinds of pleuropulmonary involvement can be distinguished in association with liver abscess, and in any individual patient there may be a progression of one complication to another. About a third of cases of pleuropulmonary amebic disease have an exudative, reactive pleural effusion, reflecting the presence of infection immediately below the diaphragm (patient 1).[1] Symptoms include cough and pleuritic chest pain, occasionally with radiation to the shoulder.[1,3,4,6] Radiographic findings of atelectasis or reactive pneumonitis may be present.[2] In the remaining two thirds of patients with pleuropulmonary disease, a hepatic abscess actually erodes into the pleural space (33% of cases), the lung parenchyma (56%) or both (12%).[1] (A third outcome, which is outside the scope of this article, is rupture into the pericardium, especially in disease involving the left lobe of the liver.[6])

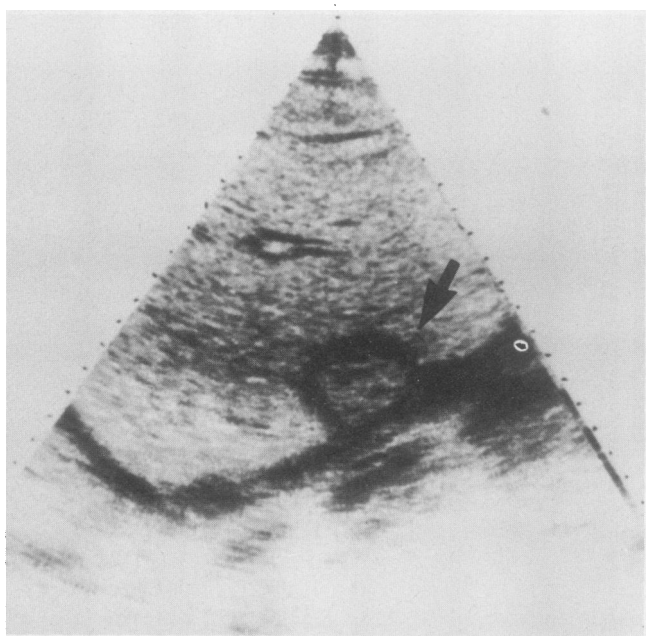

Figure 2.—Longitudinal view of a solitary amebic abscess **(arrow)** on liver ultrasonography.

Rupture into the pleural space is signaled by an abrupt worsening of pleuritic chest pain and shortness of breath (patient 2). On occasion, respiratory distress and even shock may ensue.[7] A roentgenogram of the chest may show a massive pleural effusion, occasionally with mediastinal shift.[7] The pleural fluid may be purulent or it may be greenish or dark brown, reflecting the presence of bile or digested liver tissue; amebae are detected in less than 10% of cases.[1,7]

Erosion directly into the lung parenchyma may occur with little involvement of the pleural space (patient 5). Most frequently this involves the right lower and middle lobes.[1] Rupture into a bronchus causes a dramatic clinical event with expectoration of dark-colored debris. Intense microscopic examination may show amebae, but only in a small proportion of cases.[4] A hepatobronchial fistula may lead to natural drainage of the liver abscess; alternatively, intrabronchial spread of this material may result in respiratory insufficiency.[6] Chest roentgenograms show consolidation or abscess, often with a distinctive tenting of the diaphragm,[1,3,4] sometimes called the Mexican hat sign.[1] The possibility that amebae might reach the lung via a hematogenous route[2-4] arose because intrathoracic disease was identified in some patients who did not have apparent liver involvement. The use of currently available techniques shows liver disease to be present in the vast majority of cases of intrathoracic amebiasis[1]; nevertheless, the possibility of hematogenous dissemination is supported by the rare occurrence of amebic brain abscess.[6,8]

Early misdiagnosis of amebic infections involving the pleura and lung occurs chiefly because the possibility is not considered. High-risk groups include travelers and immigrants from endemic areas (especially Mexico). Future studies may help elucidate whether homosexual men, who appear to have high rates of enteric protozoal infection,[9-11] are also at increased risk. A history of diarrheal disease, which is linked to amebic infection in the minds of most physicians, is absent in half of the patients.[2] Jaundice is unusual,[12] and hepatic function is normal or only mildly abnormal, further directing attention away from the liver.

Once the diagnosis of pleuropulmonary amebiasis is considered, further evaluation depends somewhat on the clinical presentation. If diarrhea is present, a proctoscopic examination may show changes consistent with amebiasis and the feces may contain amebic trophozoites or cysts. Sputum and pleural fluid, if present, should be closely evaluated for amebae despite the relatively low yield. Ultrasonography, liver scan or a CT scan is expected to show a liver abscess. A serum specimen should be sent for either indirect hemagglutination titers or amebic antibodies by CIE to confirm the diagnostic impression; antibody is detected in almost all patients who have invasive amebic disease and only rarely in those without parenchymal infection.

Our seven patients received metronidazole, 750 mg

every eight hours, and two of these also underwent surgical drainage; all were cured. There is some controversy over the need to use emetine hydrochoride or dehydroemetine in addition to metronidazole. Those investigators with the greatest clinical experience currently recommend that both drugs be used,[1] presumably because the success rate with one drug alone was insufficient; their data do not, however, fully support this conclusion. Others recommend the use of metronidazole alone.[6] As a result, Jones[12] concludes that metronidazole should be given together with a two- to three-day course of emetine. If extension of an amebic abscess of the liver into the chest causes acute illness, therapy with both metronidazole and emetine should be administered parenterally. The use of iodoquinol (diiodohydroxyquin) is recommended by some authorities[12] to eradicate luminal cysts, though the need to treat asymptomatic subjects who are carrying amebic cysts in their colon is open to question.

The reactive inflammatory pleuropulmonary complications respond well to treatment with amebicidal drugs, though it seems prudent to drain large effusions at the time of diagnostic thoracentesis to prevent respiratory compromise. The overall mortality of reactive pleural disease due to amebiasis was 2.5% in a large series of cases reported from Mexico.[1] Rupture into the pleural cavity with resulting amebic empyema carries a higher mortality (14.2%) and requires more aggressive therapy.[1] In addition to the administration of metronidazole, the pleural cavity must be drained by a large-bore tube to ensure adequate removal of necrotic tissue.[1,7] Rupture of the abscess into the airways may necessitate intensive respiratory support; however, with the spontaneous drainage, most patients improve on medical therapy alone.[1]

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